Calcium Channel Blockers
Therapeutic Class Review (TCR)

December 1, 2013

The literature review is current through February 19, 2016.

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

Magellan Rx MANAGEMENT℠

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Vasospastic Angina	Angina	Ventricular Rate Control	Hypertension
Dihydropyridines					
amlodipine* (Norvasc®)[1]	generic	X	X	--	X
felodipine ER (Plendil®)[2]	generic	--	--	--	X
isradipine[3]	generic	--	--	--	X
nicardipine [4]	generic	--	X	--	X
nicardipine SR (Cardene SR®)[5]	Roche	--	--	--	X
nifedipine (Procardia®)[6]	generic	X	X	--	--
nifedipine ER, nifedipine SA, nifedipine SR (Adalat CC®**, Afeditab™ CR, Nifediac CC®, Nifedical XL®, Procardia XL®)[7]	generic	X	X	--	X
nimodipine (Nymalize®)[8]***	generic	--	--	--	--
nisoldipine ER (Sular®)[9]	generic	--	--	--	X
Nondihydropyridines					
diltiazem (Cardizem®)[10]	generic	X	X	X	--
diltiazem ER (Cardizem LA®, Matzim LA™~)[11,12]	generic	--	X	--	X
diltiazem ER (Cardizem CD®, Cartia XT, Dilacor XR®, Dilt CD, Taztia XT, Tiazac®)[13]	generic	X	X	--	X
diltiazem ER (Dilt XR)[14]	generic	--	X	--	X
diltiazem ER (Diltia XT)[15]	generic	--	X	--	X
verapamil# (Calan®)[16]	generic	X	X	X	X

FDA-Approved Indications (continued)

Drug	Manufacturer	Vasospastic Angina	Angina	Ventricular Rate Control	Hypertension
Nondihydropyridines *(continued)*					
verapamil ER (Verelan PM®)[17]	generic	--	--	--	X
verapamil SR (Calan SR®, Isoptin SR®, Verelan®)[18]	generic	--	--	--	X

*amlodipine is also indicated for angiographically documented coronary artery disease (CAD) in patients without heart failure or an ejection fraction <40%.[19]

**Adalat CC is only indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents.

***nimodipine (Nymalize) oral solution is indicated only for use in subarachnoid hemorrhage.

~ Matzim LA was previously named Diltiazem LA.

#verapamil is also indicated for unstable angina.

OVERVIEW

Hypertension (HTN) affects approximately 32.6% of adult Americans and just over half of this population has their hypertension under control. From 2001 to 2011, the death rate from heart disease declined 30.8%, but inpatient cardiovascular operations and procedures increased by 28% from 2000 to 2010. Hypertension is an independent risk factor for the development of cardiovascular disease (CVD).[20] The more elevated the blood pressure, the higher the risk of myocardial infarction (MI), stroke, heart failure, and kidney disease.[21] To reduce the risk of cardiovascular (CV) events, the current blood pressure goal is less than 140/90 mm Hg.[22,23] The American Diabetes Association (ADA) suggests that the blood pressure goal for many people with diabetes and hypertension should be < 140 mmHg systolic and < 90 mmHg diastolic, but that lower systolic targets (such as < 130/80 mmHg) may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.[24] For patients with chronic renal disease, the current goal for blood pressure therapy is less than 130/80 mm Hg.[25] For patients with known coronary artery disease (CAD) or CAD equivalent, stable angina, unstable angina (UA)/non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), the target blood pressure is also less than 130/80 mm Hg.[26] Attainment of blood pressure goals results in a reduced risk of CV events.[27] There is inter-patient variability in response to various antihypertensive classes. In the absence of compelling indications, reaching target blood pressure is central in determining CV benefit in patients with hypertension, not the specific agent used.[28,29,30,31] Several trials have shown that long-acting CCBs have decreased hospitalization and subsequent revascularization procedures.[32,33,34,35]

Hypertension

CCBs have been shown to effectively reduce blood pressure. In isolated systolic hypertension (ISH), CCBs have been shown to reduce the systolic blood pressure (SBP) more than diastolic blood pressure (DBP), thereby reducing the pulse pressure. In patients with ISH, treatment with nitrendipine, a CCB not available in the U.S., reduced the stroke rate by 42% and cardiovascular morbidity by 30%.[36] In the ALLHAT study, the primary endpoint of combined fatal cardiovascular disease (CVD) and nonfatal acute

MI were similar amongst chlorthalidone, amlodipine, and lisinopril treatment arms. Amlodipine demonstrated higher risk of heart failure and hospitalization related to heart failure or fatal heart failure compared to chlorthalidone, among diabetics and non-diabetics [relative risk [RR], 1.42; 95% confidence interval (CI), 1.23 to 1.64]. CCBs and diuretics in other comparative published trials have been shown to have similar risk reductions and rates of major CVD events and stroke.[37,38,39,40,41] An ALLHAT post-hoc analysis found that in patients with metabolic syndrome, particularly in African-American patients, the findings do not support preferring a CCB, ACE inhibitor, or alpha blocker to a thiazide diuretic despite their more favorable metabolic profiles.[42] A subgroup analysis of ALLHAT showed that despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, cardiovascular disease outcomes in older hypertensive adults with metabolic syndrome, as compared with treatment with CCBs and ACE inhibitors.[43] A post-hoc analysis of the ALLHAT data demonstrated a higher risk of heart failure with amlodipine and lisinopril versus chlorthalidone in the first year. The unadjusted risk of hospitalized or fatal heart failure remained higher for amlodipine versus chlorthalidone (RR, 1.35; 95% CI, 1.21 to 1.5) and lisinopril (RR, 1.23; 95% CI, 1.09 to 1.38).[44]

Several large clinical trials have compared CCBs with other types of antihypertensives. Some of the trials in patients with hypertension include ALLHAT, VALUE, INVEST, CONVINCE, and ASCOT-BPLA.[45,46,47,48,49] The comparator antihypertensives have included ACE inhibitors, diuretics, angiotensin receptor blockers, beta-blockers, and combinations of antihypertensives. Many of these large trials have demonstrated that CCBs have beneficial effects on composite cardiovascular outcomes or individual clinical outcomes. However, most of the trials only demonstrate equivalence to the comparator antihypertensives rather than superiority.[50,51,52]

In The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), published in 2003, diuretics were recommended as first-line agents.[53] Since the publication of JNC-7 guidelines for the treatment of hypertension, a meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attack, stroke and death in patients taking HCTZ has been published.[54] Based on 14 studies including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium antagonists. Additionally, the meta-analysis concluded that there are no studies or evidence that HCTZ reduces myocardial infarction, stroke, or death. As a result, the Eighth Report from the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) suggests that ACE inhibitors, ARBs, thiazides, or calcium channel blockers (CCBs) may be used as first-line therapy for patients with hypertension.[55] In African-American patients, CCBs and thiazides are recommended first-line.

Angina

The 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines, and the American Association for Thoracic Surgery (AATS), Preventive Cardiovascular Nurses Association (PCNA), Society for Cardiovascular Angiography (SCAI) and Interventions, and Society of Thoracic Surgeons (STS) focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease recommend the use of a CCB for relief of anginal symptoms if there are contraindications or adverse reactions to beta blockers.[56] Likewise, CCBs may be added to beta blockers for relief of anginal symptoms if additional therapy is needed.

CCBs improve clinical symptoms and are well tolerated. Long-acting CCBs are recommended. Vasospastic (or Prinzmetal's) angina is effectively treated with CCBs by reducing the frequency of anginal attacks.

PHARMACOLOGY[57,58]

CCBs inhibit calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The reduction in afterload, which results in a decrease in myocardial oxygen consumption, is thought to be responsible for the CCB benefit in angina. There are three classes of CCBs: diphenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and dihydropyridines (e.g., amlodipine, felodipine ER, isradipine, nicardipine, nifedipine, and nisoldipine ER). The dihydropyridines are potent vasodilators and can increase or have a neutral effect on vascular permeability.[59] The nondihydropyridine verapamil, and to a lesser extent, diltiazem, are less potent vasodilators, but they have a greater depressive effect on cardiac conduction and contractility.

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
Dihydropyridines				
amlodipine (Norvasc)[60]	64-90	30-50	Inactive metabolites	Urine: 60
felodipine ER (Plendil)[61]	20	11-16 for immediate release	Six inactive metabolites; concentration is 23% of parent	Urine: 70 Feces: 10
nicardipine/SR (Cardene/SR)[62,63]	35	11.5	Metabolized extensively	Urine: 60 Feces: 35
nifedipine (Procardia/XL)[64, 65]	40-77 (Procardia) 86 (Procardia XL relative to IR)	2	Inactive metabolites	Urine: 60-80
nimodipine[66]	13	1-2	Inactive metabolites	--
nimodipine (Nymalize)[67]	13	1-2	Inactive metabolites	--
nisoldipine ER (Sular)[68]	5	7-12	5 metabolites; one active, 10% activity of parent; concentration equal to parent	Urine: 60-80
nisoldipine ER new formulation (Sular)[69]	5	13.7	5 metabolites; one active, 10% activity of parent; concentration equal to parent	Urine: 60-80
Nondihydropyridines				
diltiazem (Cardizem)[70]	40-60	3.5-9	desacetyl diltiazem is 25-50% as potent as parent; concentration is 10-20% of parent	--
diltiazem ER (Cardizem LA, Matzim LA)[71, 72]	40	6-9	desacetyl diltiazem is 25-50% as potent as parent; concentration is 10-20% of parent	--
diltiazem ER (Cardizem CD)[73]	--	5-8	--	--
verapamil (Verelan PM)[74]	33-65 (varies with rate and extent of release from dosage forms)	4.5-20	13 metabolites; norverapamil is 20% as potent as parent; concentration equal to parent	Urine: 70-74 Feces: 16

Chronotherapeutics is the concept of administering antihypertensives by delayed release mechanisms to lower blood pressure during the rapid rise associated with awakening. It is unclear if this concept actually lowers morbidity and mortality.[75]

CONTRAINDICATIONS/WARNINGS

Nicardipine is contraindicated in patients with advanced aortic stenosis. Reduction of DBP in these patients may worsen rather than improve myocardial oxygen balance.[76] Peripheral edema is a common adverse event of CCBs and usually occurs within two to three weeks of starting therapy.

Short-acting nifedipine has been related to increased coronary mortality rates in patients with a history of MI and should not be used for the treatment of hypertension.[77,78]

Diltiazem and verapamil are contraindicated in sick sinus syndrome (except in patients with a functioning artificial pacemaker), second or third degree atrioventricular block (except in patients with a functioning artificial pacemaker), hypotension (SBP<90 mm Hg), or cardiogenic shock. Diltiazem is contraindicated in acute myocardial infarction (MI) and pulmonary congestion. Verapamil is contraindicated in severe left ventricular dysfunction, atrial flutter or fibrillation with an accessory bypass tract (Wolff-Parkinson-White syndrome or Lown-Ganong-Levine syndrome). Diltiazem and verapamil should be used with caution in hepatic or renal dysfunction.[79,80,81,82,83]

Nimodipine capsules nor liquid should not be administered intravenously or by any other parenteral method as this could result in death.[84] Short-acting nifedipine has been related to increased coronary mortality in patients with a history of MI and should not be used for the treatment of hypertension.[85,86]

There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of Procardia XL (GITS tablet formulation). Bezoars can occur in very rare cases and may require surgical intervention.[87] Risk factors for a gastrointestinal obstruction identified from post-marketing reports of Procardia XL include alteration in gastrointestinal anatomy (e.g., severe gastrointestinal narrowing, colon cancer, small bowel obstruction, bowel resection, gastric bypass, vertical banded gastroplasty, colostomy, diverticulitis, diverticulosis, and inflammatory bowel disease), hypomotility disorders (e.g., constipation, gastroesophageal reflux disease, ileus, obesity, hypothyroidism, and diabetes) and concomitant medications (e.g., H2-histamine blockers, opiates, nonsteroidal anti-inflammatory drugs, laxatives, anticholinergic agents, levothyroxine, and neuromuscular blocking agents). Cases of tablet adherence to the gastrointestinal wall with ulceration have been reported, some requiring hospitalization and intervention.

DRUG INTERACTIONS

Nifedipine and nisoldipine should not be administered with grapefruit juice.[88,89,90] Nifedipine ER and Felodipine ER may increase tacrolimus serum levels.[91,92]

Nifedipine is metabolized by CYP3A4 and co-administration along with phenytoin lowers the systemic exposure by approximately 70%. Avoid use with phenytoin or any known inducer of CYP3A4 or consider an alternative antihypertensive therapy.[93]

Blood pressure lowering effects may be additive when used concurrently with sildenafil (Viagra®, Revatio™), tadalafil (Cialis®, Adcirca™), and vardenafil (Levitra®).

Diltiazem and verapamil both inhibit CYP3A4; both can increase the effects of amiodarone, beta-blockers, lithium, digoxin, carbamazepine, and selected HMG-CoA reductase inhibitors (statins). For statins given with diltiazem, limit the dose of simvastatin to 10 mg daily and diltiazem to 240 mg daily. For statins coadministered with verapamil, limit the dose of simvastatin to 10 mg daily and lovastatin to 40 mg daily.

Amlodipine is a CYP3A4 substrate. Coadministration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.[94]

Grapefruit juice can increase verapamil serum concentrations, and to a lesser extent, diltiazem serum concentrations.[95,96,97,98,99]

Cardiovascular action of other CCBs may be enhanced by the addition of nimodipine.[100]

ADVERSE EFFECTS

Drug	AV Block	Constipation	Dizziness	Edema	Fatigue	Flushing	HA	Nausea
Dihydropyridines								
amlodipine (Norvasc)[101] n=1,730 (placebo n=1,250)	nr	< 1	1.1-3.4 (1.5)	1.8–10.8 (0.6)	4.5 (2.8)	0.7 – 2.6 (0)	nr	2.9 (1.9)
felodipine ER (Plendil)[102] n=861 (placebo n=334)	nr	0.3 – 1.5 (0.9)	2.7 – 3.7 (2.7)	2 – 17.4 (3.3)	nr	3.9 – 6.9 (0.9)	10.6 – 14.7 (10.2)	1 – 1.7 (1.5)
isradipine IR[103]	nr	nr	7.3 (4.4)	7.2 (3)	3.9 (0.3)	2.6 (0)	13.7 (14.1)	1.8 (1.7)
nicardipine[104,105] n=1,390 (placebo n=211)	nr	0.2-0.6 (0-0.6)	1.8-4 (0)	0.3-8 (0-1.4)	nr	2.1-9.7 (0-2.8)	2.6-8.2 (0-4.7)	0.9-2.2 (0-0.9)
nicardipine SR (Cardene SR)[106,107] n=322 (placebo n=140)	nr	nr	1.6 (0.7)	5.9 (1.4)	nr	nr	6.2 (7.1)	1.9 (0.7)
nifedipine (Procardia) [108] n=226 (placebo n=235)	nr	<2	27 (15)	7 (1)	nr	25 (8)	23 (20)	11 (8)
nifedipine SR (Procardia XL)109 n=707 (placebo n=266)	nr	3.3 (2.3)	4.1 (4.5)	10 – 30	5.9 (4.1)	< 3	15.8 (9.8)	3.3 (1.9)
nimodipine110, 111, 112* n=823 (placebo n=479)	nr	nr	<1	0.4-1.2 (0.6)	nr	nr	1.2-1.4 (0.2)	0.6-1.2 (0)
nisoldipine ER (Sular)113 n=663 (placebo n=280)	≤ 1	nr	3-7 (4)	7-27 (10)	nr	nr	22 (15)	2 (1)

Adverse Effects (continued)

Drug	AV Block	Constipation	Dizziness	Edema	Fatigue	Flushing	HA	Nausea
Nondihydropyridines								
diltiazem ER (Cardizem LA, Matzim LA)[114, 115]	3.2	< 1	6.4	6.8	4.8	1.4	4.6	1.4
diltiazem ER (Cardizem CD) [116] n=607	3.3 (0)	< 1	3 (3)	2.6 (1.3)	nr	1.4	5.4 (5)	1.4
verapamil ER (Verelan PM)[117,118] n=297 (placebo n=116)	nr	8.8 (0.9)	3 (0.9)	1.7 (0)	nr	nr	12.1 (11.2)	1.7 (0)

*The safety and efficacy of Nymalize, nimodipine oral solution in the treatment of patients with SAH is based on adequate and well-controlled studies of nimodipine oral capsules in patients with SAH.[119]

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

SPECIAL POPULATIONS

Pediatrics

Amlodipine has been studied in a randomized, double-blind, placebo-controlled, parallel-group study with 268 hypertensive children (mean age, 12.1 ± 3.3 years).[120] Amlodipine reduced blood pressure in a dose-dependent manner with good tolerability, and only 2% of children discontinued therapy related to adverse effects. The effective antihypertensive oral dose of amlodipine in pediatric patients aged six to 17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.[121]

Safety and efficacy of other CCBs in hypertensive pediatrics have not been established.[122] Many of the CCBs are extended release products, making them difficult to use in children.

Pregnancy

All products in this class are Pregnancy Category C.[123]

Hepatic/Renal Impairment

Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine ER, diltiazem, and verapamil may require dose adjustment in hepatic impairment or in cirrhosis. Nicardipine, diltiazem, and verapamil may require dose adjustment in renal impairment.[124]

Geriatrics

Age appears to have an effect on the pharmacokinetics of nifedipine. The clearance is reduced resulting in higher area under the curve (AUC)in the elderly and are not due to changes in renal function.[125]

DOSAGES

Drug	Initial HTN Dose	Maximum HTN Dose	Angina Dose	Availability
Dihydropyridines				
amlodipine (Norvasc)[126]	5 mg daily	10 mg daily	5-10 mg daily	2.5, 5, 10 mg tablets
felodipine ER (Plendil)[127]	5 mg daily	10 mg daily	--	2.5, 5, 10 mg tablets
isradipine[128]	2.5 mg twice daily	10 mg twice daily	--	2.5, 5 mg capsules
nicardipine[129]	20 mg three times a day	40 mg three times a day	20-40 mg three times a day	20, 30 mg capsules
nicardipine SR (Cardene SR)[130]	30 mg twice daily	60 mg twice daily	--	30, 45 mg capsules
nifedipine[131]	--	--	10 mg three times a day to max of 30 mg per dose or 180 mg per day	10, 20 mg capsules
nifedipine SR[132]	Adalat CC, Procardia XL: 30-60 mg daily	Adalat CC: 90 mg Procardia XL: 120 mg daily	Adalat CC, Procardia XL: 30-90 mg daily	ER tablet: 30, 60, 90 mg tablets Adalat CC, Procardia XL, Nifediac CC: 30, 60, 90 mg tablets Afeditab CR, Nifedical XL: 30, 60 mg tablets
nimodipine (Nymalize)[133]	--	--	--	30 mg capsules 16 oz (473 mL) bottle 20 mL unit dose cup with 1 oral syringe
nisoldipine ER[134]	20 mg daily	60 mg daily	--	ER tablet: 20, 30, 40 mg tablets
nisoldipine ER (Sular)[135]	17 mg daily	34 mg daily	--	8.5, 17, 25.5, 34 mg tablets (new formulation)

Nimodipine, including Nymalize oral solution, is administered as 60 mg every four hours for 21 days for the reduction of the incidence and severity of ischemic deficits associated with subarachnoid hemorrhage.[136] Administer Nymalize enterally (oral, nasogastric, gastric) and not intravenously or by other parenteral routes.

Nisoldipine ER generic tablets and Sular tablets are not AB-rated and are not interchangeable.

Dosages (continued)

Drug	Initial HTN Dose	Maximum HTN Dose	Angina Dose	Availability
Nondihydropyridines				
diltiazem (Cardizem)[137]	--	--	30 mg four times daily to a max of 360 mg per day	30, 60, 90, 120 mg tablets
diltiazem ER[138,139]	120-240 mg daily	480 mg daily Tiazac: 540 mg daily	120-480 mg daily Tiazac: 120-540 mg daily	ER capsules: 60, 90, 120, 180, 240, 300, 360, 420 mg capsules Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Dilt CD, Dilt XR, Taztia XT, Tiazac: 120, 180, 240 mg capsules Cardizem CD, Cartia XT, Dilt CD, Taztia XT, Tiazac: 300 mg capsules Cardizem CD, Taztia XT, Tiazac: 360 mg capsules Tiazac: 420 mg capsules
diltiazem ER (Cardizem LA, Matzim LA)[140,141]	180-240 mg daily	540 mg daily	180-360 mg daily	120, 180, 240, 300, 360, 420 mg tablets
verapamil (Calan)[142]	80 mg three times daily	480 mg per day	80 mg-120 mg three times daily up to a max of 480 mg per day	40, 80, 120 mg tablets
verapamil ER (Verelan PM)[143]	200 mg at bedtime	400 mg at bedtime	--	100, 200, 300 mg capsules
verapamil SR[144]	240 mg daily	480 mg daily	--	Calan SR, Isoptin SR: 120, 180, 240 mg tablets
verapamil SR (Verelan)[145]	240 mg daily	480 mg daily	--	120, 180, 240, 360 mg capsules

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. Comparative clinical trials have been performed with some of the agents in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of

manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many clinical studies were performed in the 1980 and 1990s evaluating the hemodynamic effects of the CCBs; however, clinical trials with clinical endpoints have more recently been published. The literature review of significant trials comparing agents within this therapeutic class is complete as of February 19, 2016.

amlodipine (Norvasc) and nicardipine (Cardene)

Amlodipine and nicardipine were compared in a randomized, double-blind trial evaluating efficacy in 133 patients with ISH.[146] Patients were over 60 years old. Patients were randomized to amlodipine 5 mg once daily or nicardipine 60 mg per day (given in two or three divided doses). Doses were titrated up if necessary for BP control with maximum doses of amlodipine 10 mg daily and nicardipine 100 mg per day given in divided doses. After 90 days, the office blood pressure and ambulatory blood pressure monitoring (ABPM) were significantly reduced in terms of SBP and pulse pressure by both therapies. Per ABPM studies, amlodipine had a greater effect on the SBP than nicardipine. Therapy was well tolerated.

amlodipine (Norvasc) and nisoldipine ER (Sular)

In a randomized, double blind, double-dummy, parallel group trial, amlodipine and nisoldipine ER were compared for efficacy, safety, and tolerability in 120 patients with stage one to two hypertension (DBP of 90 to 109 mm Hg) and chronic stable angina.[147] The initial phase was a three-week placebo run-in phase followed by the randomization to nisoldipine ER 20 or 40 mg once daily or amlodipine 5 or 10 mg once daily. Doses were titrated if needed after two weeks to achieve a DBP of less than 90 mm Hg. At six weeks, nisoldipine ER (-15/-13 mm Hg) and amlodipine (-13/-11 mm Hg) effectively reduced blood pressure (p=NS). Blood pressure response rates for nisoldipine ER (87%) and amlodipine (78%) were similar (p=NS). The mean increase in total exercise time was similar in both groups (p=NS). More headache and peripheral edema were observed with nisoldipine ER, but overall, both therapies were well tolerated.

Nisoldipine ER and amlodipine were compared in 192 African-American patients with DBP of 95 to 114 mm Hg over 12 weeks.[148] Patients were randomized to nisoldipine ER 20 to 60 mg daily or amlodipine 5 to 10 mg daily in a double-blind manner. Blood pressure, using ambulatory monitoring, was significantly lower compared to baseline with nisoldipine ER (-23/-16 mm Hg) and amlodipine (-20/-15 mm Hg) (between-group comparisons, p=0.07 for SBP; p=0.5 for DBP). Neither agent had an effect on heart rate. Adverse effects were similar for both groups; most commonly reported were headache, edema, and dizziness.

diltiazem ER (Cardizem LA) and amlodipine (Norvasc)

Diltiazem ER and amlodipine were compared in 262 hypertensive African-Americans in a multicenter, randomized, double-blind, parallel-group, dose-to-effect study.[149] Patients were randomized to diltiazem ER 360 mg at bedtime (10 p.m.) or morning amlodipine 5 mg (8 a.m.) for six weeks; if blood pressure still exceeded 130/85 mm Hg, therapy was titrated to diltiazem ER 540 mg or amlodipine 10 mg. Changes in blood pressure, heart rate, and rate-pressure product (heart rate x SBP) were measured by ambulatory blood pressure monitoring for the first four hours after awakening and over a 24-hour period. Amlodipine increased heart rate whereas diltiazem ER decreased heart rate. Greater

mean reductions in heart rate and rate-pressure product were seen in the diltiazem group during all intervals (p≤0.0008). Diltiazem ER showed greater reductions in DBP during the first four hours after awakening and between 6 a.m. and noon (p<0.0049 and p<0.0019), but had a comparable reduction in the mean 24-hour DBP to amlodipine. Reductions in the SBP in the morning hours were comparable for both groups; however, amlodipine demonstrated a 3.4 mm Hg greater reduction in the mean 24-hour SBP (p<0.0022). Both arms were well tolerated. The manufacturer of diltiazem ER funded the study.

felodipine ER (Plendil) and amlodipine (Norvasc)

In a multicenter, double-blind, parallel group trial, felodipine ER and amlodipine were compared in 535 elderly hypertensive patients (> 65 years).[150] Patients had an initial sitting DBP of 90 to 115 mm Hg or SBP of 160 to 220 mm Hg. Patients were randomized to felodipine ER 2.5 mg or amlodipine 5 mg once daily. Blood pressure was evaluated after three and six weeks; if BP reduction was not satisfactory, doses were titrated upward. After nine weeks, the average doses of felodipine ER and amlodipine were 5.5 mg and 7.3 mg. The primary endpoint of new vasodilatory adverse effects was reported by 32% of the felodipine ER group and 43% of the amlodipine group (p=0.007). Both treatments effectively reduced blood pressure 24 hours post-dose.

felodipine ER (Plendil) and nisoldipine ER (Sular)

A multicenter, randomized, double-blind trial compared the safety and efficacy of nisoldipine ER 20 to 40 mg daily and felodipine ER 5 to 10 mg daily in 229 patients with mild to moderate hypertension.[151] Following a two-week placebo run-in phase, patients were randomized and followed for 16 weeks. Both drugs demonstrated significant reductions in blood pressure compared to baseline. No significant differences in blood pressure reduction were observed between the two drugs. The percentage of responders was 77.8 and 66.5% for nisoldipine ER and felodipine ER, respectively, Edema occurred more frequently with nisoldipine ER (30%) compared to felodipine ER (21%). More patients withdrew from the nisoldipine ER group than felodipine ER group with the most common reason being edema.

nifedipine gastrointestinal therapeutic system (GITS)

The ACTION trial was a randomized, double-blind trial evaluating the effects of nifedipine GITS on long-term outcome in 7,665 patients with stable angina.[152] Patients with stable CAD were randomized to nifedipine GITS 60 mg daily or placebo. The primary endpoint, the composite of death, acute MI, refractory angina, new overt heart failure, debilitating stroke, or peripheral revascularization, was similar in both groups {nifedipine 4.6 per 100 patient-years; 4.75 per 100 patient-years for placebo (0.97 [0.88 to 1.07], p=0.54)}. With nifedipine GITS, rate of death and any cardiovascular event or procedure was 9.32 per 100 patient-years versus 10.50 per 100 patient-years for placebo (0.89 [0.83 to 0.95], p=0.0012). Fewer patients underwent coronary angiography and interventions with nifedipine GITS.

nifedipine CC and amlodipine (Norvasc)

A total of 207 patients were enrolled in a randomized, double-blind parallel-group study to compare the antihypertensive efficacy and safety of nifedipine coat-core 30 mg to amlodipine 5 mg.[153] After four weeks of double-blind therapy, patients with a trough seated DBP ≥ 90 mm Hg received an increased dose of nifedipine coat-core 60 mg or amlodipine 10 mg. In the patients with available data (n=176), mean blood pressure decreased from 160.9/101.9 mm Hg to 141.3/85.5 mm Hg in the

nifedipine group and from 160.5/101.8 mm Hg to 140.7/85.9 mm Hg in the amlodipine group. Both drugs were well tolerated, with equivalent antihypertensive efficacy, and similar safety profiles.

nisoldipine ER (Sular)

The NICOLE study determined the effects of nisoldipine ER on the rate of progression of coronary atherosclerosis and the rate of clinical cardiovascular events.[154] The single-center, double-blind, randomized, placebo-controlled study enrolled 826 patients who had undergone coronary angioplasty. Patients were randomized to nisoldipine ER 40 mg daily or placebo and followed for up to three years. No significance difference was observed between the groups for the number of new coronary lesions. The average minimum luminal diameter of the non-dilated coronary lesions decreased in both groups; however, the difference between the groups was not significant. Both groups demonstrated progression of atherosclerosis in at least one coronary arterial segment, which was defined as an increase in diameter stenosis of ≥ 13%. Rates of death, stroke, and MI were similar between the groups; however, revascularizations were less frequent with nisoldipine ER. Therefore, nisoldipine ER patients had overall fewer clinical events compared to placebo (44.6 versus 52.6%, p=0.02).

controlled-onset extended release verapamil (Covera-HS) and nifedipine GITS (Procardia XL)

In a prospective, double-blind, randomized trial to compare 24-hour blood pressure control, controlled-onset extended release verapamil and nifedipine GITS were administered to 557 hypertensive patients over ten weeks.[155] Dose titration was based on blood pressure readings at baseline, four weeks, and ten weeks. The four-hour time period of one hour prior to awakening to three hours after awakening was the focus of intense evaluation. Early morning blood pressure was reported to be similar between the two groups. Nifedipine GITS lowered blood pressure significantly more during sleep (-11 mm Hg in the nifedipine GITS group versus -5.8 mm Hg in the verapamil group). Both drugs effectively reduced blood pressure throughout 24 hours. Covera-HS has since been removed from the market.

chronotherapeutic oral drug absorption system (CODAS) verapamil (Verelan PM)

In a randomized, double-blind, placebo-controlled trial, CODAS verapamil was evaluated for efficacy in blood pressure reduction in 277 patients with mild to moderate hypertension.[156] All patients received placebo for two to four weeks prior to randomization. During the run-in placebo phase, patients must have had an initial sitting DBP of 95 to 115 mm Hg. Patients were then randomized in a double-blind manner to CODAS verapamil of 100, 200, 300, or 400 mg or placebo to be taken between 9 p.m. and 11 p.m. for eight weeks. Blood pressure was measured weekly and ambulatory blood pressure monitoring was obtained. The 200, 300, and 400 mg doses of CODAS verapamil were effective in lowering DBP compared to placebo. Blood pressure reductions were the greatest between 6 a.m. and noon. Dose-dependent blood pressure reductions were observed. Adverse events were reflective of other verapamil preparations.

META-ANALYSIS

A meta-analysis of 13 major studies with nearly 104,000 pooled hypertensive patients suggests that the dihydropyridine CCBs were associated with a lower risk of stroke compared to other randomized antihypertensives (p=0.006).[157]

SUMMARY

The benefits of calcium channel blockers (CCBs) in controlling angina and hypertension are clearly documented. No CCB has demonstrated a clinical advantage over other CCBs in the treatment of hypertension. The dihydropyridine CCBs cause a baroreceptor-mediated reflex increase in heart rate because of their potent peripheral vasodilating effects. Diltiazem decreases atrioventricular conduction and heart rate. Verapamil decreases heart rate, slows atrioventricular nodal conduction to the greatest extent of the CCB and is useful for supraventricular tachyarrhythmias.

The Eighth Report from the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) suggests that ACE inhibitors, ARBs, thiazides, or CCBs may be used as first-line therapy for patients with hypertension. In African-American patients, CCBs and thiazides are recommended first-line. CCBs should generally be used in combination with other antihypertensive agents in high-risk cardiovascular disease (CVD) patients and diabetics. Short-acting nifedipine has been related to increased coronary mortality rates in patients with a history of myocardial infarction and should not be used for the treatment of hypertension.

The effect on cardiovascular morbidity and mortality with CCBs compared to other agents such as diuretics and angiotensin-converting enzyme (ACE) inhibitors had been less clear until the ALLHAT study, which enrolled patients with hypertension with a known risk factor for coronary artery disease (CAD), showed that chlorthalidone, amlodipine, and lisinopril had similar outcomes of combined fatal CVD and nonfatal MI.

Several trials, such as the CAMELOT study in patients with CAD and normal blood pressure, the NICOLE study in patients with coronary atherosclerosis, and the ACTION study in patients with CAD and stable angina, have demonstrated decreased hospitalization and revascularization procedures associated with several long-acting CCBs.

Many large trials enrolling patients with hypertension, including ALLHAT, VALUE, INVEST, CONVINCE, and ASCOT-BPLA, have demonstrated that CCBs have beneficial effects on composite cardiovascular outcomes or individual clinical outcomes; however, most of the trials only demonstrate equivalence to the comparator antihypertensives rather than superiority.

REFERENCES

1 Norvasc [package insert]. New York, NY; Pfizer; January 2013.
2 Plendil [package insert]. Wilmington, DE; AstraZeneca; October 2012.
3 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
4 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
5 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
6 Procardia [package insert]. New York, NY; Pfizer, July 2013.
7 Procardia XL [package insert]. New York, NY; Pfizer; July 2013.
8 Nymalize [package insert]; Atlanta GA; Arbor Pharmaceuticals; May 2013
9 Sular [package insert]. Atlanta, GA; Shionogi Pharma, Inc.; January 2013.
10Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
11 Cardizem LA [package insert]. Mississauga, ON; Biovail; November 2010.
12 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
13 Cardizem CD [package insert]. Bridgewater, NJ; Biovail; November 2009.
14 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
15 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
16 Calan [package insert]. New York, NY; Pfizer; October 2013.
17 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
18 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
19 Norvasc [package insert]. New York, NY; Pfizer; January 2013.

20 American Heart Association. Heart Disease and Stroke Statistics – 2015 Update. Available at: http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/2014-Publications_UCM_471037_Article.jsp. Accessed February 22, 2016.
21 Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardio. 2014; Jul 18. pii: S0735-1097(14)04510-0 and Circulation 2014; 128 Available at: http://circ.ahajournals.org/content/early/2014/07/25/CIR.0000000000000095. Accessed February 22, 2016.
22 Rosendorff C, Lackland, DT, Allison M, et al. AHA/ACC/ASH Scientific Statement: treatment of hypertension in patients with coronary artery disease. Hypertension. 2015; 65: 1372-1407. DOI: 10.1161/HYP.0000000000000018. Available at: http://hyper.ahajournals.org/content/65/6/1372. Accessed February 22, 2016.
[23] Go AS, Bauman M, Coleman King SM, Fonarow GC, Lawrence W, Williams KA, Sanchez E. An Effective Approach to High Blood Pressure Control. AHA/ACC/CDC Science Advisory, JACC 2013, DOI: 10.1016/j.jacc.2013.11.007. Available at: http://content.onlinejacc.org/article.aspx?articleid=1778408. Accessed February 22, 2016.
24 American Diabetes Association. Standards of medical care in diabetes – 2016. Diabetes Care. 2016. Diabetes Care. 2016 39 (Suppl 1) S1-S112. Available at: http://care.diabetesjournals.org/site/misc/2016-Standards-of-Care.pdf. Accessed February 22, 2016.
25 National Kidney Foundation Guidelines. KDOQI clinical practice guideline on hypertension and antihypertensive agents in chronic kidney disease: Kidney Disease Outcome Quality Initiative. Am J Kidney Dis. 2004; 43(suppl 1):S16-S33. Available at: http://www.kidney.org/professionals/KDOQI/guidelines_commentaries. Accessed February 22, 2016.
26 Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014; Jul 18. pii: S0735-1097(14)04510-0 and Circulation 2014; 128 Available at: http://circ.ahajournals.org/content/early/2014/07/25/CIR.0000000000000095. Accessed February 22, 2016.
27 James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 2014, 311 (5): 507-520. Available at: http://jama.jamanetwork.com/article.aspx?articleid=1791497. Accessed February 22, 2016.
28 Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014; Jul 18. pii: S0735-1097(14)04510-0 and Circulation 2014; 128 Available at: http://circ.ahajournals.org/content/early/2014/07/25/CIR.0000000000000095. Accessed February 22, 2016.
29 Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Journal of Hypertension. 2013; 31:1281–1357. Available at: http://www.esh2013.org/wordpress/wp-content/uploads/2013/06/ESC-ESH-Guidelines-2013.pdf. Accessed February 22, 2016.
30 Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of random trials. Arch Intern Med. 2005; 165(12):1410-1419.
31 Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. J Hypertens. 2003; 21(6):1055-1076.
32 Nissen SE, Tuzcu M, Libby P, et al. Effect of Antihypertensive Agents on Cardiovascular Events in Patients with Coronary Disease and Normal Blood Pressure. The CAMELOT study: a randomized controlled trial. JAMA. 2004; 292(18):2217-2226.
33 Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet. 2004; 364(9437):849-57.
34 Dens JA, Desmet WJ, Coussement P, et al. Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. Heart. 2003; 89(8):887-92.
35 Kizer JR, Kimmel SE. Epidemiologic review of the calcium channel blocker drugs. An up-to-date perspective on the proposed hazards. Arch Intern Med. 2001; 161(21):1145-1158.
36 Staessen JA, Fagard R, Thijs L, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350:757-764.
37 Staessen JA, Fagard R, Thijs L, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350:757-764.
38 Hansson L, Lindholm LH, Ekborn T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999; 354:1751-1756.
39 Hansson L, Hedner T, Lund-Johansen P, et al for the NORDIL Study Group. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet. 2000; 356(9227): 359-65.
40 Pahor M, Psaty BM, Alderman MH, et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. Lancet. 2000. 356(9246):1949-1954.
41 Neal B, MacMahon S, Chapman N. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium channel antagonists, and other blood pressure lowering drugs: results of prospectively designed overviews of randomised trials. Lancet. 2000; 356(9246):1955-1964.
42 Wright JT, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2008; 168(2):207-217.
43 Black HR, Davis B, Barzilay J, et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Diabetes Care. 2008; 31(2):353-360.
44 Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation. 2006; 113(18):2201-2210.

45 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288:2981-2997.
46 Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004; 363(9426):2022-31.
47 Pepine CJ, Handberg EM, Cooper-De Hoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003; 290(21):2805-16.
48 Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA. 2003; 289(16):2073-82.
49 Dahlof B, Sever PS, Poulter NR, et al for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005; 366:895-906.
50 Mahmud A, Feely J. Low-dose quadruple antihypertensive combination: more efficacious than individual agents-a preliminary report. Hypertension. 2007; 49(2):272-275.
51 Kjeldsen SE, Julius S, Mancia G, et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertension. 2006; 24(7):1405-1412.
52 Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. J Hypertension. 2006; 24(11):2163-2168.
53 Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure and the National High Blood Pressure Education program Coordinating Committee. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA. 2003; 289:2560-2572.
54 Messerli FH, Makani H, Benjo A, et al. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. J Am Coll Cardiol. 2011; 57:590-600.
55 PaulA. James, MD; Suzanne Oparil, MD; Barry L. Carter PharmD., et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5):507-520. DOI:10.1001/jama.2013.284427
56 Fihn SD, Blankship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014; 64(18): 1929.DOI: 10.1016/j.jacc.2014.07.017. Available at: http://circ.ahajournals.org/content/130/19/1749. Accessed February 24, 2016.
57 Grossman E, Messerli FH. Calcium antagonists. Prog Cardiovasc Dis. 2004; 47(1):34-57.
58 Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. Am J Med. 2004; 116(1):35-43.
59 DRUGDEX® System [Internet database]. Greenwood, Colo: Thompson Micromedex. Updated periodically.
60 Norvasc [package insert]. New York, NY; Pfizer; January 2013.
61 Plendil [package insert]. Wilmington, DE; AstraZeneca; October 2012.
62 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
63 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
64 Procardia [package insert]. New York, NY; Pfizer, July 2013.
65 Procardia XL [package insert]. New York, NY; Pfizer; July 2013.
66 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
67 Nymalize [package insert] Atlanta GA; Arbor Pharmaceuticals; May 2013
68 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
69 Sular [package insert]. Atlanta, GA; Shionogi Pharma, Inc.; January 2013.
70 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
71 Cardizem LA [package insert]. Mississauga, ON; Biovail; November 2010.
72 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
73 Cardizem CD [package insert]. Bridgewater, NJ; Biovail; November 2009.
74 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
75 Cooke-Ariel, H. Circadian variations in cardiovascular function and their relation to the occurrence and timing of cardiac events. Am J Health-Syst Pharm. 1998; 55(Suppl 3):S5-11.
76 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
77 Grossman E, Messerli FH, Grodzicki T, et al. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA. 1996; 276:1328-1331.
78 Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation. 1995; 92:1326-1331.
79 Calan [package insert]. New York, NY; Pfizer; October 2013.
80 Covera-HS [package insert]. New York, NY; Pfizer; October 2011.
81 Cardizem LA [package insert]. Mississauga, ON; Biovail; November 2010.
82 Cardizem CD [package insert]. Bridgewater, NJ; Biovail; November 2009.
83 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
84 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
85 Grossman E, Messerli FH, Grodzicki T, et al. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA. 1996; 276:1328-1331.
86 Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation. 1995; 92:1326-1331.
87 Procardia XL [package insert]. New York, NY; Pfizer; July 2013.

88 Procardia [package insert]. New York, NY; Pfizer, July 2013.
89 Procardia XL [package insert]. New York, NY; Pfizer; July 2013.
90 Sular [package insert]. Atlanta, GA; Shionogi Pharma, Inc.; January 2013.
91 Procardia XL [package insert]. New York, NY; Pfizer; July 2013.
92 Plendil [package insert]. Wilmington, DE; AstraZeneca; October 2012.
93 Procardia [package insert]. New York, NY; Pfizer, July 2013.
94 Norvasc [package insert]. New York, NY; Pfizer; January 2013.
95 Calan [package insert]. New York, NY; Pfizer; October 2013.
96 Covera-HS [package insert]. New York, NY; Pfizer; October 2011.
97 Cardizem LA [package insert]. Mississauga, ON; Biovail; November 2010.
98 Cardizem CD [package insert]. Bridgewater, NJ; Biovail; November 2009.
99 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
100 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
101 Norvasc [package insert]. New York, NY; Pfizer; January 2013.
102 Plendil [package insert]. Wilmington, DE; AstraZeneca; October 2012.
103 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
104 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
105 Facts and Comparisons on-line. Version 4.0; Wolters Kluwer Health, Inc.; 2011. Accessed January 31, 2011.
106 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
107 Facts and Comparisons on-line. Version 4.0; Wolters Kluwer Health, Inc.; 2011. Accessed January 31, 2011.
108 Procardia [package insert]. New York, NY; Pfizer, July 2013.
109 Procardia XL [package insert]. New York, NY; Pfizer; July 2013.
110 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
111 Facts and Comparisons on-line. Version 4.0; Wolters Kluwer Health, Inc.; 2011. Accessed January 31, 2011.
112 Nymalize [package insert], Atlanta GA; Arbor Pharmaceuticals; May 2013
113 Sular [package insert]. Atlanta, GA; Shionogi Pharma, Inc.; January 2013.
114 Cardizem LA [package insert]. Mississauga, ON; Biovail; November 2010.
115 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
116 Cardizem CD [package insert]. Bridgewater, NJ; Biovail; November 2009.
117 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
118 Facts and Comparisons on-line. Version 4.0; Wolters Kluwer Health, Inc.; 2011. Accessed January 31, 2011.
119 Nymalize [package insert], Atlanta GA; Arbor Pharmaceuticals; May 2013.
120 Flynn JT, Newburger JW, Daniels SR, et al for the PATH-1 Investigators. A randomized, placebo-controlled trial of amlodipine in children with hypertension. J Pediatr. 2004; 145(3):353-359.
121 Norvasc [package insert]. New York, NY; Pfizer; January 2013.
122 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
123 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
124 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
125 Procardia [package insert]. New York, NY; Pfizer, July 2013.
126 Norvasc [package insert]. New York, NY; Pfizer; January 2013.
127 Plendil [package insert]. Wilmington, DE; AstraZeneca; October 2012.
128 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
129 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
130 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
131 Procardia [package insert]. New York, NY; Pfizer, July 2013.
132 Procardia XL [package insert]. New York, NY; Pfizer; July 2013.
133 Nymalize [package insert], Atlanta GA; Arbor Pharmaceuticals; May 2013
134 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
135 Sular [package insert]. Atlanta, GA; Shionogi Pharma, Inc.; January 2013.
136 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
137 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
138 Cardizem CD [package insert]. Bridgewater, NJ; Biovail; November 2009.
139 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
140 Cardizem LA [package insert]. Mississauga, ON; Biovail; November 2010.
141 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
142 Calan [package insert]. New York, NY; Pfizer; October 2013.
143 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
144 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
145 Available at: http://clinicalpharmacology.com. Accessed February 24, 2016.
146 Mounier-Vehier C, Jaboureck O, Emeriau JP, et al. Randomized, comparative, double-blind study of amlodipine vs. nicardipine as a treatment of isolated systolic hypertension in the elderly. Fundam Clin Pharmacol. 2002; 16(6):537-544.
147 Pepine CJ, Cooper-De Hoff RM, Weiss RJ, et al. Comparison of effects of nisoldipine-extended release and amlodipine in patients with systemic hypertension and chronic stable angina pectoris. Am J Cardiol. 2003; 91(3):274-279.
148 White WB, Saunders E, Noveck RJ, et al. Comparative efficacy and safety of nisoldipine extended-release (ER) and amlodipine (CESNA-III study) in African American patients with hypertension. Am J Hypertens. 2003; 16(9):739-745.
149 Wright JT Jr, Sica DA, Gana TJ, et al. Antihypertensive efficacy of night-time graded-release diltiazem versus morning amlodipine in African Americans. Am J Hypertens. 2004; 17(9):734-742.

150 Schaefer RM, Aldons PM, Burgess ED, et al. Improved tolerability of felodipine compared with amlodipine in elderly hypertensives: a randomised, double-blind study in 535 patients, focusing on vasodilatory adverse events. The International Study Group. Int J Clin Pract. 1998; 52(6):381-386.
151 Hoglund C, Hutchinson HG. A comparison of nisoldipine coat-core and felodipine in the treatment of mild to moderate hypertension. Int J Clinical Practice. 1998; 52:221-225.
152 Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet. 2004; 364(9437):849-857.
153 Zidek W, Spiecker C, Knaup G, et al. Comparison of the efficacy and safety of nifedipine coat-core versus amlodipine in the treatment of patients with mild-to-moderate essential hypertension. Hypertension Study Group. Clin Ther. 1995; 17:686-700.
154 Dens JA, Desmet WJ, Coussement P, et al. Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. Heart. 2003; 89(8):887-892.
155 White WB, Black HR, Weber MA, et al. Comparison of effects of controlled onset extended release verapamil at bedtime and nifedipine gastrointestinal therapeutic system on arising on early morning blood pressure, heart rate, and the heart rate-blood pressure product. Am J Cardiol. 1998; 81:424-431.
156 Smith DH, Neutel JM, Weber MA. A new chronotherapeutic oral drug absorption system for verapamil optimizes blood pressure control in the morning. Am J Hypertens. 2001; 14:14-19.
157 Angeli F, Verdecchia P, Reboldi GP, et al. Calcium channel blockade to prevent stroke in hypertension: a meta-analysis of 13 studies with 103,793 subjects. Am J Hypertens. 2004; 17(9):817-822.